# CASE REPORTS

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## Remission of Acute Myelogenous Leukemia Complicating Waldenström Macroglobulinemia

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THE DEVELOPMENT of acute myelogenous leukemia (AML) in patients with independent hematopoietic disorders has been well documented and recently reviewed.[1] In more than 70 reported cases, multiple myeloma has developed in patients with AML.[2-5] In most of these cases, the leukemia was preceded by chemotherapy with alkylating agents. AML has also been described in six patients with Waldenström macroglobulinemia,[6-11] a disease similar to multiple myeloma. Before AML developed, five of these patients received chemotherapy for the gammopathy.

The acute leukemia complicating multiple myeloma or Waldenström macroglobulinemia has generally been refractory to treatment. In our review of the literature, 36 of 74 multiple myeloma patients with AML received antileukemic chemotherapy, with achievement of complete remission in only one patient.[12] Of the six patients with AML complicating Waldenström macroglobulinemia, three died without antileukemic treatment[6,8,9] and three underwent induction therapy with failure to achieve complete remission.[7,10,11]

In this report we describe attainment of complete remission from AML in a patient with Waldenström macroglobulinemia.

### Report of a Case

A 42-year-old asymptomatic white man had blood which was found to be difficult to crossmatch for blood donation in 1963. Laboratory values included a hematocrit of 37 percent and a leukocyte count of 5,600 per cu mm. Rare atypical lymphocytes with plasmacytoid characteristics were noted in the peripheral smear. Serum protein electrophoresis showed a sharp M-component spike of 2.8 grams per dl. Utracentrifugation showed a pronounced increase in 19S macroglobulins. Bone marrow examination showed a normal myeloid-erythroid ratio, normal myelopoiesis, and a pleomorphic increase in plasmacytoid lymphocytes. Results of additional studies included negative findings on Coombs, latex fixation and cold agglutinin tests. On physical examination no adenopathy, abdominal organomegaly or other abnormalities were noted. A radiograph of the chest and skeletal survey showed no abnormalities. Waldenström macroglobulinemia was diagnosed and the case was followed without treatment until 1966.

At that time, the presence of fatigue, bleeding, anemia and increasing serum IgM suggested progression of the gammopathy. Chlorambucil was administered each day for five years, to a cumulative dose of 7.3 grams. In 1971 a total of 168 mg of melphalan and 1.9 grams of prednisone was given over three months. During the following five years, the patient received 29 courses of cyclophosphamide, vincristine and prednisone (cumulative doses of 51 grams of cyclophosphamide, 217 mg of vincristine and 252 grams of prednisone) ending in July, 1976.

Over the subsequent six months, progressive pancytopenia was noted. Red cell production was decreased with simultaneously increased sequestration of $^{51}$Cr-labeled red blood cells in liver and spleen. Falling platelet and erythrocyte counts

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were not improved by high dose steroids. A left-shifted myeloid line with reduced maturation appeared in the bone marrow. Both the immature myeloid cells and previously observed plasmacytoid lymphocytes were increased relative to other marrow elements. Small numbers of myeloblasts appeared in the peripheral blood. Serum muramidase was 24 μg per ml (normal value 5 to 10). The serum IgM, previously stable at 1.6 grams per dl, rose to 2.1 grams per dl. The patient's course was interpreted to represent early AML and increased activity of the macroglobulinemia.

In an attempt to diminish splenic sequestration of platelets and erythrocytes, splenectomy was carried out in February of 1977. Splenic histology showed an intense proliferation of myeloblasts. The leukocyte count was 5,000 per cu mm with 9 percent polymorphonuclear leukocytes, 10 percent band forms, 4 percent metamyelocytes, 26 percent myeloblasts, 52 percent lymphocytes, 3 percent monocytes, 4 percent eosinophils and 2 percent basophils; the platelet count was 14,000. In the marrow there was pronounced progression of the myeloblastic proliferation with poor myeloid maturation; a diagnosis of AML was confirmed. A 10-day course of induction therapy was carried out with daunorubicin, cytosine arabinoside and 6-thioguanine, as previously described.[13] Marrow hypoplasia was observed 14 days after treatment was begun. In addition to supportive therapy with multiple antibiotics, the patient received red blood cell, platelet and granulocyte transfusions. Three weeks after the last chemotherapy a marrow examination and a peripheral blood count confirmed complete remission with M1 status.[14] The leukocyte count was 10,600 per cu mm with 51 percent polymorphonuclear leukocytes, 13 percent band forms, 6 percent metamyelocytes, 21 percent lymphocytes and 9 percent monocytes. The hematocrit was 34 percent and the platelet count 370,000. The serum IgM was stable at 1.4 grams per dl.

Monthly doses of cytosine arabinoside and 6-thioguanine were subsequently given for maintenance therapy.[13] Three months after attaining remission, the peripheral leukocyte count was 9,000 per cu mm with 42 percent polymorphonuclear leukocytes, 10 percent band forms, 5 percent metamyelocytes, 32 percent lymphocytes and 11 percent monocytes. The hematocrit was 30 percent and the platelet count was 300,000. The patient's bone marrow was normocellular and showed normal number and maturation of hematopoietic lines. However, the marrow now also contained 60 percent plasmacytoid lymphocytes. The serum IgM was elevated to 3.2 grams per dl. Further therapy for the gammopathy was initiated. Four and a half months after attaining remission the patient's AML relapsed. The patient declined further chemotherapy.

## Discussion

Acute myelogenous leukemia is recognized as a delayed consequence of antineoplastic chemotherapy, particularly when alkylating agents are used, as reviewed by several authors.[1,15-19] Reimer and co-workers have recently shown that ovarian cancer patients, if treated with alkylating agents, have an increased relative risk of AML developing.[20] An association of AML with Hodgkin disease treated by radiation with and without chemotherapy was reviewed by Rosner and Grunwald.[21] The development of AML in patients with multiple myeloma is discussed in many publications.[1-5] In a series recently reported by Gonzales, Trujillo and Alexanian the incidence of AML in melphalan-treated patients with multiple myeloma was found to be approximately 100 times higher than in normal subjects.[5] Alkylating agents have been specifically implicated as leukemogens in multiple myeloma because the increased incidence of acute leukemia in this group was not noted before the advent of alkylator therapy.[4,22] In the present case and in five of six previously reported cases of AML complicating Waldenström macroglobulinemia, alkylator treatment preceded diagnosis of leukemia.[6-10]

The AML complicating multiple myeloma and Waldenström macroglobulinemia has shown a particularly poor prognosis. Of the 36 reported multiple myeloma patients treated for AML, in only one was complete leukemic remission achieved.[12] Similarly, in the three patients with Waldenström macroglobulinemia previously given induction therapy for AML, complete remission was not reached.[7,10,11]

Despite this prior negative experience, in our patient a complete remission of the AML was obtained in the presence of Waldenström macroglobulinemia. Our successful treatment of AML is in contrast to even the most recent experience of Gonzales, Trujillo and Alexanian with six patients with multiple myeloma.[5] In our patient, activity of the Waldenström macroglobulinemia remained stable during antileukemic treatment

but began to progress three months following leukemic remission.

The reason for our successful treatment in this case is speculative. The two gammopathies may differ in their effect upon a person's ability to undergo antileukemic induction. The chemotherapy and supportive care used during induction was more intense than the treatment given in many previously reported cases of gammopathy with AML.

Mutagenesis by alkylating agents may account for leukemogenesis with this group of patients. An increased frequency of chromosomal aberrations has been noted in acute leukemias which follow alkylator treatment in myeloma patients.[5,23] Immunosuppression by alkylators may lead to leukemia. In this setting malignant clones may proliferate in a more permissive environment.

Alternatively, the increased survival of treated patients may itself enable us to observe acute leukemias developing in multiple myeloma and Waldenström macroglobulinemia. Any intrinsic predisposition to acute leukemia in these lymphoid disorders would more likely be expressed during a longer lifetime. Indeed, AML has developed in at least three cases of multiple myeloma[24,25] and one case of Waldenström macroglobulinemia[11] with no previous chemotherapy.

Coexistence in the bone marrow of two independent hematopoietic neoplasms presents potential problems for therapy. *A priori,* elimination of AML could provide a less competitive and more favorable setting for proliferation of the gammopathy. The treatment of AML involves induction of marrow aplasia with subsequent repopulation by "nonleukemic" cell lines. In the presence of Waldenström macroglobulinemia and prior chemotherapy, this preservation and replication of stem cells must take place in an altered and potentially less favorable marrow environment. However, as shown in our case, adequate stem cells are retained, and their proliferation permitted marrow regeneration.

Achievement of remission from AML in our patient with Waldenström macroglobulinemia should encourage future efforts to treat acute leukemia complicating the gammopathies.

## Summary

In a patient with Waldenström macroglobulinemia acute myelogenous leukemia developed after treatment with alkylating drugs for ten years. Chemotherapy led to complete remission of the leukemia. Activity of the monoclonal gammopathy, as judged by serum IgM and bone marrow infiltrate, increased three months after leukemic remission was attained. This is the first reported successful induction of acute myelogenous leukemia in a patient with Waldenström macroglobulinemia. Although acute myelogenous leukemia complicating the gammopathies is frequently refractory to therapy, complete remission is possible.

### REFERENCES

1. Bloomfield DC, Brunning RD: Acute leukemia as a terminal event in nonleukemic hematopoietic disorders. Semin Oncology 3: 297-317, Sep 1976

2. Rosner F, Grunwald H: Multiple myeloma terminating in acute leukemia: Report of 12 cases and review of the literature. Am J Med 57:927-939, Dec 1974

3. Karchmer RK, Amare M, Larsen WE, et al: Alkylating agents as leukemogens in multiple myeloma. Cancer 33:1103-1107, Apr 1974

4. Kyle RA, Pierre RV, Bayrd ED: Multiple myeloma and acute leukemia associated with alkylating agents. Arch Intern Med 135: 185-191, Jan 1975

5. Gonzalez F, Trujillo JM, Alexanian R: Acute leukemia in multiple myeloma. Ann Intern Med 86:440-443, Apr 1977

6. Videbaek A: Unusual cases of myelomatosis. Br Med J 2: 326, May 1971

7. Forbes IJ: Development of acute leukemia in Waldenström macroglobulinemia after prolonged treatment with chlorambucil. Med J Austral 1:918-919, Apr 1972

8. MacKenzie MR, Fudenberg HH: Macroglobulinemia: An analysis of forty patients. Blood 39:874-889, Jun 1972

9. Söndergaard Petersen H: Erythroleukemia in a melphalan-treated patient with primary macroglobulinemia. Scan J Haematol 10:5-11, Feb 1973

10. Cardamone JM, Kimmerle RI, Marshall EV: Development of acute erythroleukemia in B-cell immunoproliferative disorders after prolonged therapy with alkylating drugs. Am J Med 57:836-842, Nov 1974

11. Salberg K, Kurtides ES, McKeever WP: Monomyelocytic leukemia in an untreated case of Waldenström macroglobulinemia. Arch Intern Med 37:514-516, Apr 1977

12. Mills RC, Cornwell GG, McIntyre OR: Remission of leukemia associated with multiple myeloma. N Engl J Med 285:920-921, Oct 1971

13. Embury SH, Elias L, Heller PH, et al: Remission maintenance therapy in acute myelogenous leukemia. West J Med 126: 267-272, Apr 1977

14. Hewlett JS, Battle JD, Bishop RC, et al: Phase II study of A-8103 (NSC-25154) in acute leukemia in adults. Cancer Chemother Rep 42:25-28, Nov 1964

15. Holland JF: Epidemic acute leukemia. N Engl J Med 283: 1165-1166, Nov 1970

16. Leukaemia and cytotoxic drugs (Editorial). Lancet 1:70-71, Jan 1971

17. Penn I: Second malignant neoplasms associated with immunosuppressive medications. Cancer 37:1024-1032, Feb 1976

18. Rosner F: Acute leukemia as a delayed consequence of cancer chemotherapy. Cancer 37:1033-1036, Feb 1976

19. Therapy-linked leukaemia. Lancet 1:519-520, Mar 1977

20. Reimer RR, Hoover R, Fraumeni JF, et al: Acute leukemia after alkylating-agent therapy of ovarian cancer. N Engl J Med 297:177-181, Jul 1977

21. Rosner F, Grünwald H: Hodgkin's disease and acute leukemia: Report of eight cases and review of the literature. Am J Med 58:339-353, Mar 1975

22. Berg JW: The incidence of multiple primary cancers—I. Development of further cancers in patients with lymphomas, leukemias, and myeloma. J Nat Cancer Inst 38:741-752, May 1967

23. Hossfeld DK, Holland JF, Cooper RG, et al: Chromosome studies in acute leukemias developing in patients with multiple myeloma. Cancer Res 35:2808-2813, Oct 1975

24. Parker AC: A case of acute myelomonocytic leukemia associated with myelomatosis. Scand J Haematol 11:257-260, Nov 1973

25. Tursz T, Flandrin G, Brouet JC, et al: Simultaneous occurrence of acute myeloblastic leukemia and multiple myeloma without previous chemotherapy. Br Med J 2:642-643, Jun 1974